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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

AF 1600
PATENT

In re Application of: Petros Karouzakis

Application No.: 09/762,602

Group No.: 1617

Filed: 03/21/2001

Examiner: Hui

For: Use of Misoprostol and/or Metabolites of Misoprostol for Treating Sexual Dysfunction in Women

**RESPONSE UNDER
37 C.F.R. § 1.116
EXPEDITED PROCEDURE
EXAMINING GROUP
1617**

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT OR RESPONSE AFTER FINAL REJECTION--TRANSMITTAL

1. Transmitted herewith is an amendment after final rejection (37 C.F.R. 1.116) for this application.

CERTIFICATION UNDER 37 C.F.R. §§ 1.8(a) and 1.10*

(When using *Express Mail*, the *Express Mail* label number is **mandatory**;
Express Mail certification is optional.)

I hereby certify that, on the date shown below, this correspondence is being:

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Signature

Date: December 15, 2003

Robert M. Asher
(type or print name of person certifying)

* Only the date of filing (§ 1.6) will be the date used in a patent term adjustment calculation, although the date on any certificate of mailing or transmission under § 1.8 continues to be taken into account in determining timeliness. See § 1.703(f). Consider "Express Mail Post Office to Addressee" (§ 1.10) or facsimile transmission (§ 1.6(d)) for the reply to be accorded the earliest possible filing date for patent term adjustment calculations.

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STATUS

2. Applicant is other than a small entity.

EXTENSION OF TERM

3. The proceedings herein are for a patent application and the provisions of 37 C.F.R. 1.136 apply. Applicant petitions for an extension of time under 37 C.F.R. 1.136 (fees: 37 C.F.R. 1.17(a)(1)-(4)) for one month:

Fee: \$110.00

FEE FOR CLAIMS

4. The fee for claims (37 C.F.R. 1.16(b)-(d)) has been calculated as shown below:

	(Col.1)		(Col. 2)	(Col. 3)	OTHER THAN A SMALL ENTITY	
	Claims Remaining After Amendment		Highest No. Previously Paid For	Present Extra	Rate	Addit Fee
Total	22	Minus	22	= 0	x \$18 =	\$0
Indep	4	Minus	4	= 0	x \$86 =	\$0
First Presentation of Multiple Dependent Claim					+ \$290 =	\$0
Total						\$0
Addit. Fee						

No additional fee for claims is required.

FEE PAYMENT

5. Attached is a check in the amount of \$290.00, including fee of \$180.00 for filing Information Disclosure Statement after Issuance of Final Office Action.

Charge any additional fees required by this paper or credit any overpayment in the manner authorized above.

A duplicate of this paper is attached.

FEE DEFICIENCY

6.

If any additional extension and/or fee is required, charge Account No. 19-4972.

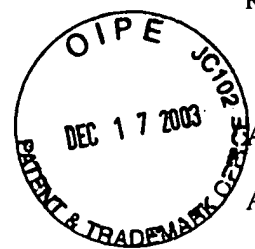
If any additional fee for claims is required, charge Account No. 19-4972.

Date: December 15, 2003



Robert M. Asher
Registration No. 30,445
Bromberg & Sunstein LLP
125 Summer Street
Boston, MA 02110-1618
US
617-443-9292
Customer No. 02101

01581/00128 285561.1



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Petros Karouzakis et al.

Att'y Docket: 1581/128

App. No.: 09/762,602

Art Unit: 1617

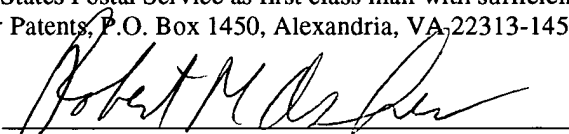
Filing Date: March 21, 2001

Examiner: Hui

For: Use of Misoprostol and/or Metabolites of Date: December 15, 2003
Misoprostol for Treating Sexual Dysfunction in Women

CERTIFICATE OF MAILING

I hereby certify that this document, along with any other papers referred to as being attached or enclosed, is being deposited with the United States Postal Service as first class mail with sufficient postage in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on **December 15, 2003.**


Robert M. Asher

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RESPONSE TO FINAL OFFICE ACTION

(Expedited Procedure - - Technology Center 1617)

Sir:

In response to the Final Office Action mailed September 5, 2003, Applicants submit information and arguments herewith that effectively traverse the pending rejection of the claims.

Interview Summary

Applicants thank the Examiner for the courtesy of speaking with Applicants' attorney on November 4, 2003. Applicants' counsel focused on the Examiner's conclusions with respect to obviousness that were made "absent evidence to the contrary." Applicants' counsel explained that early tests (March 6, 1999) with respect to the male sexual dysfunction drug Viagra, showed that it was little if any benefit to women with sexual dysfunction. While the Examiner acknowledged that this was the sort of evidence that he

would find persuasive, he indicated a preference for information as of the time of the priority date of Applicants' invention.

Submission of New Information

We now submit evidence showing that as of the priority date, yohimbine, one of the therapeutically active compounds identified by Nahoum, while effective in men produced no therapeutic response in women. The Examiner's assumption that the therapeutically active compounds identified by Nahoum would be effective in women was not justified. The yohimbine tests demonstrate that when Nahoum listed therapeutically active compounds, there was no basis for expecting therapeutic results in women suffering from sexual dysfunction. The references cited in the rejection do not overcome the shortcomings of Nahoum. Only Applicants' work has demonstrated the effectiveness of misoprostol for treating women with sexual dysfunction.

Rejection over Combination of Six References

Claims 27-31, 33-42, 50-54 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Lowrey, Neal, Nahoum, Buyuktimkin et al. in view of El-Rashidy and Reilly. "A critical step in analyzing the patentability of claims pursuant to §103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the 'then accepted' wisdom in the field." *In re Kotzab*, 217 F. 3d, 1365, 1369, 55 U.S.P.Q. 2d 1313 (Fed. Cir. 2000). The Examiner improperly attributes more to accepted wisdom than can be supported by the references. At page 8 of the rejection, the Examiner sets forth a teaching that he finds within the primary references. Applicants strongly disagree that the references show any indication that misoprostol and alprostadil are known to be used in female sexual dysfunction treatment. Successful treatment of females is very different from men, making the Examiner's conclusions unjustified.

A case of *prima facie* obviousness has not been made out by the Examiner. The Examiner argues that Nahoum teaches misoprostol and alprostadil are useful in treating female sexual dysfunction. Nahoum states that an H₃ agonist is used for treating male and

female sexual dysfunction. While Nahoum states that the H₃ agonist may be combined with a therapeutically active agent, there is no indication from Nahoum's long list of such agents, which ones are effective in females. Nahoum provides a general list of facilitators, potentiating agents and erectogenic agents. The references lack any suggestion or teaching to one skilled in the art for pulling out from that list misoprostol other than making use of the Applicant's experimentation in Applicant's own application. Nor can one find incentive for applying misoprostol topically to the clitoris or vagina of a female suffering from the dysfunction. Nahoum merely supplies a general list filled with pitfalls. Nahoum gave no incentive for selecting a particular list member for use with females and, in particular, no incentive for using misoprostol.

While misoprostol is among the listed therapeutically active compounds in Nahoum, so are compounds believed to be ineffective in treating female sexual dysfunction. Yohimbine is on the list. (Col. 10, l. 10). Nahoum gives no information to those of skill in the art for distinguishing the effectiveness of any given one of the therapeutically active compounds listed. Applicants submit that given the absence of test results with respect to any given compound, effectiveness with respect to female sexual dysfunction was unpredictable and undisclosed. Applicants submit herewith an article entitled "Yohimbine for Erectile Dysfunction." This article concluded that yohimbine medication was beneficial for use in treating erectile dysfunction in men. A second article entitled "Plasma MHPG Response to Yohimbine Treatment In Women with Hypoactive Sexual Desire" is enclosed herewith. This article, published in a January-March 1998 *Journal of Sex and Marital Therapy* concluded that women demonstrated no therapeutic response to yohimbine. Thus, it is no more correct to conclude from Nahoum that yohimbine was known for use in female sexual dysfunction than it would be to conclude that misoprostol was known to be useful in female sexual dysfunction treatment.

To whatever extent the prior art references teach use of specific vasodilators in the treatment of male sexual dysfunction, there is no corresponding teaching that these compounds have a reasonable expectation of being effective in the treatment of female sexual dysfunction. A finding of obviousness requires that the prior art show a reasonable expectation of success. *Amgen, Inc. v. Chugai Pharmaceuticals Co., Ltd.*, 18 U.S.P.Q. 2d

1016, 1022 (Fed. Cir. 1991). At best, Nahoum provides a general list but no guidance for selecting a compound that can produce the desired result of treating female sexual dysfunction. "A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out." *In re Deuel*, 51 F.3d 1552, 1559, 34 U.S.P.Q. 2d 1210 (Fed. Cir. 1995). Given that Nahoum provides no test results (let alone successful results) on female subjects and no discussion of topical administration to the clitoris or vagina, there is no teaching of Applicants' method nor a showing that it would be expected to succeed.

Applicants provide further support for the proposition that treatments which successfully treat erectile dysfunction in men cannot on that basis alone provide a reasonable expectation of successful treatment of sexual dysfunction in women as of the time of the filing, of the priority patent application. Several months after the priority application was filed, a first preliminary study was conducted on the blockbuster drug Viagra which was known and approved for use in treating erectile dysfunction in men. Enclosed herewith is the "Study: Viagra Ineffective for Female Sexual Dysfunction" published March 6, 1998 indicating that Viagra proved to provide little if any benefit to women in the first preliminary study. Even now, an anecdotal report (enclosed) from June 2003 issue of Boston Magazine quotes Dr. Irwin Goldstein who said with regard to finding a pill for use in treating female sexual dysfunction "Probably a decade away... There will be a pill. But that day is not tomorrow. We are nowhere near understanding what is happening in women."

Referring now to the claims, claim 27 recites using misoprostol or misoprostol acid as a primary vasoactive agent for topical administration to the clitoris or vagina of the female subject in need of a treatment for sexual dysfunction. The references as a whole fail to teach or disclose this invention. Neal is solely directed to treatment of male erectile dysfunction. It fails to provide a reasonable expectation of success with respect to female sexual dysfunction. Nahoum teaches formulations for use in treating both male and female sexual dysfunction. However, the primary active in Nahoum's formulation is H₂ and H₃ agonists. While Nahoum lists a number of vasoactive agents that may be used in conjunction with the primary active, there is no suggestion or disclosure that any one of these vasoactive agents

should replace the primary. Nor is there any reasonable expectation of success with any listed therapeutic agent for use in the treatment of female subjects for sexual dysfunction. Lowrey only suggests that oral administration helpful in male sexual dysfunction might be tried in females. With respect to female subjects, in example 5, Lowrey gives a mere prophetic example suggesting that one might try using the oral formulation. As we know from the experiments with Viagra and yohimbine, lacking tests on female subjects, the disclosure of Lowrey provides no reasonable expectation of success for any given male treatment on females.

The Examiner concedes that “the primary references do not expressly teach the application of the topical prostaglandin composition in a method of treating female sexual dysfunction to the vagina or clitoris.” Applicants respectfully submit that neither is there an implicit suggestion or teaching of topical administration to the vagina or clitoris of a formulation whose primary vasoactive agent is misoprostol or misoprostol acid. The remaining references also lack these teachings. Buyuktimkin does not relate to the treatment of sexual dysfunction in males or females. El-Rashidy lacks any discussion of the treatment of females or female sexual dysfunction. Reilly also does not discuss sexual dysfunction treatment. In view of the art cited by the Examiner as a whole and considering the state of knowledge with regard to treatment of female sexual dysfunction at the time of the invention, the invention as claimed in claim 27 and all claims depending therefrom should be allowed.

Not only is there no teaching of the methods of claims 27-31 and 33-40 but the wisdom at the time taught away from using misoprostol in a topical administration to females. As set forth in the patent application at page 7, l. 13-15, the Physician’s Desk Reference recognized that misoprostol causes irritation of smooth urethral fibers. This raises concerns for using misoprostol in touch with the genital system of pregnant women. At certain dosage levels, it could cause miscarriage. Thus, not only are the claims nonobvious, but the art at the time made misoprostol an unlikely candidate for topical treatment of women with sexual dysfunction. Claims 27-31 and 33-40 should be allowed.

Claims 41 and 42 more broadly recite use of a mixture including misoprostol or misoprostol acid in the treatment of sexual dysfunction in a female subject. The only

references of the six cited by the Examiner to discuss treatment of female sexual dysfunction are Lowrey and Nahoum. Lowrey merely suggests oral administration of a composition. Nahoum discloses a variety of compositions for possible combination with the primary actives H₂ and H₃ agonists. While misoprostol is on a list of available therapeutically active compounds, so is yohimbine. Nahoum does not provide sufficient information for one skilled in the art to identify misoprostol for effectiveness in the treatment of female sexual dysfunction. Indeed, misoprostol's irritative characteristics teach away from its use. At best, Nahoum provides a general suggestion that one may try any of a number of compositions for treating females. Nahoum does not disclose any results with respect to treating female sexual dysfunction. Given all the pitfalls in Nahoum's list, only hindsight or undue experimentation might lead specifically to misoprostol. No test results (let alone successful results) are given for female subjects, there is no teaching of Applicant's method nor showing that it would be expected to succeed. Lowrey discloses oral administration. Lowrey does not teach, disclose or suggest topical administration. Lowrey does not establish a reasonable expectation of success for topical administration to females. Successful topical procedures for sexual dysfunction in the references were directed to the male penis, a sex organ surrounded by skin and having a urethra therein. The cited prior art references fail to disclose success with topical administration to treat female sexual dysfunction, nor do they provide incentive to use misoprostol. None of the other references overcome the shortcomings of Nahoum and Lowrey, therefore the topical treatments with misoprostol for women in claims 41 and 42 should be allowed.

Claims 50-54 have been misinterpreted by the Examiner. The Examiner cites Buyuktimkin as disclosing the use of penetration enhancer compositions along with prostaglandin E₁. Claims 50-54 on the other hand lack a non-misoprostol penetration enhancer. Instead, the composition for topical administration in Claim 50 employs the misoprostol or/and misoprostol acid to facilitate penetration to underlying tissue. None of the references cited by the Examiner suggest using misoprostol or/and misoprostol acid to facilitate penetration of vasoactive agents to the underlying tissues. The misoprostol or/and misoprostol acid advantageously serve both functions as penetration enhancement and vasoactive agent. In the Office Action of January 10, 2003, the Examiner indicated that "the

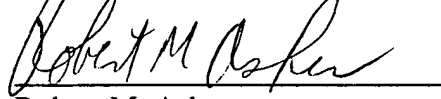
data demonstrates the effectiveness of misoprostol formulation, in absence of any organic solvent or penetration enhancer, to be more effective than that of prostaglandin E₁.” This was established by the declaration of Mr. Fotinos. Claims 50-54 are allowable for these reasons in addition to all those reasons set forth above with regard to the failure of the cited references to show or suggest that misoprostol would have been reasonably expected to be effective in the treatment of female sexual dysfunction and in particular that the treatment be carried out through topical administration to the clitoris or vagina.

Rejection over Nahoum

Claims 48 and 49 stand rejected under 35 U.S.C. §103 as being unpatentable over Nahoum. Claims 48 and 49 recite a pharmaceutical composition including misoprostol compound and alprostadil wherein penetration of the alprostadil to underlying tissues is facilitated by the misoprostol compound. This synergic action is taught by the inventors at the bottom of page 3 of the patent application and is neither taught, disclosed or suggested by Nahoum. Nahoum does not teach as the Examiner states that misoprostol and alprostadil are useful for treating female sexual dysfunction. Rather, Nahoum specifically discloses treating male and female sexual dysfunction with a H₃ agonist which may be combined with a second therapeutically active compound. Nahoum does not disclose or suggest using two therapeutically active compounds nor in particular misoprostol and alprostadil in combination with the H₃ agonist. Moreover in the treatment of female sexual dysfunction Nahoum does not disclose selecting any particular one of the erection producing agents, facilitators or potentiating agents in the list of therapeutically active compounds. Neither is there any indication from Nahoum that misoprostol and alprostadil could be used beneficially in combination such that the misoprostol facilitates penetration of the alprostadil. Rather, Nahoum refers those of skill in the art to penetration enhancers such as “DMSO, bile acid salts, modified bile-acid salts, propylene glycol and polyethylene glycol analogs.” Col. 15, l. 59-60. Thus, the benefit of facilitating penetration of the alprostadil through the combination with misoprostol compound has not been shown to be expected in view of the disclosure of Nahoum. This further demonstrates the lack of incentive to make a topical formulation from misoprostol and alprostadil. For these reasons, Applicants submit that the composition of claims 48 and 49 are not obvious in view of Nahoum.

For all the foregoing reasons, Applicants submit that the present application is in condition for allowance and early notice to that effect is respectfully solicited.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Robert M. Asher", is written over a horizontal line.

Robert M. Asher

Reg. No. 30,445

Bromberg & Sunstein LLP

125 Summer Street, 11th Floor

Boston, MA 02110-1618

(617) 443-9292

Attorney for Applicants

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